AMENDED SPECIFICATION

Reprinted as amended in accordance with the decision of the Superintending Examiner acting for the Comptroller-General, dated the twenty-first day of August, 1957, under Section 29, of the Patents Act, 1949.

PATENT SPECIFICATION

767,824

Inventor: WALTER JOSEPH TINDALL

Date of filing Complete Specification: July 29, 1954.

Application Date: Aug. 26, 1953. *No. 23616/53.*

Complete Specification Published: Feb. 6, 1957.

Index at acceptance:—Class 81(1), B1(F: G: N: R: Z), L1.

International Classification:—A61k.

COMPLETE SPECIFICATION

ERRATA

AMENDED SPECIFICATION No. 767,824

Page 2, line 35, *for* "partally" *read* "partially"
Page 3, line 69, *for* "be" *read* "beta"

THE PATENT OFFICE,
13*th January*, 1958.

treatment of skin complaints such as eczema or promoting healing of wounds.

As applied for cosmetic purposes the preparations according to the invention aim at stimulating and replacing the epidermis, thus minimising or reducing the effects of ageing, especially preventing the dehydration and atrophy which are basically the cause of the changes seen in ageing skin.

Cosmetic creams have been available on the market which contain oestrogens, such as oestrone, oestradiol and stilboestrol and while such preparations have been effective to some extent in reducing wrinkles and reducing the other effects of ageing, mainly by stimulating epidermal skin mitosis, their use has been attended by the risk of undesirable side i.e. such as show substantially no activity in stimulating the secondary sex organs, are very effective for the purpose outlined above, and that, in consequence of the absence of sexual activity the disadvantages previously encountered in such preparations are avoided.

In accordance with the present invention a preparation for the treatment of human skin consists of a vehicle capable of being spread on the skin containing as active ingredient a steroid compound which is virtually free from male or female sexual activity as herein defined, and is a derivative of Δ^5-androsten-3β-ol or of Δ^4-androsten-3-one or of androstan-3β-ol or of androstan-3-one, substituted at C17 with a keto group or a hydroxyl group (in either alpha or beta position), with or

[*Price 3s. 6d.*]

Price 4s 6

AMENDED SPECIFICATION

Reprinted as amended in accordance with the decision of the Superintending Examiner acting for the Comptroller-General, dated the twenty-first day of August, 1957, under Section 29, of the Patents Act, 1949.

PATENT SPECIFICATION

Inventor: WALTER JOSEPH TINDALL

767,824

Date of filing Complete Specification: July 29, 1954.

Application Date: Aug. 26, 1953. *No. 23616/53.*

Complete Specification Published: Feb. 6, 1957.

Index at acceptance:—Class 81(1), B1(F: G: N: R: Z), L1.

International Classification:—A61k.

COMPLETE SPECIFICATION

Improvements in preparations for the Treatment of the Human Skin

We, ORGANON LABORATORIES LIMITED, a British Company, of Brettenham House, Lancaster Place, London, W.C.2, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to improvements in preparations for the treatment of the human skin and to methods for producing such preparations. Such preparations are primarily intended for cosmetic purposes for improving the personal appearance particularly in the case of ageing or senile skin, but they also have medicinal applications, for example, for the treatment of burns, for encouraging the growth of skin grafts, for the treatment of skin complaints such as eczema or promoting healing of wounds.

As applied for cosmetic purposes the preparations according to the invention aim at stimulating and replacing the epidermis, thus minimising or reducing the effects of ageing, especially preventing the dehydration and atrophy which are basically the cause of the changes seen in ageing skin.

Cosmetic creams have been available on the market which contain oestrogens, such as oestrone, oestradiol and stilboestrol and while such preparations have been effective to some extent in reducing wrinkles and reducing the other effects of ageing, mainly by stimulating epidermal skin mitosis, their use has been attended by the risk of undesirable side effects particularly on the uterus and breast and with the possibility of activating early malignant changes.

Another disadvantage of these substances is that the stimulation of the skin mitosis is only temporary; for example it has been found that after about two weeks' application cessation of the stimulation occurs. This effect appears to be due to the increased size of the adrenal cortex induced by the oestrogen and it is known that the cessation of mitosis can be brought about by the adrenal hormones. Furthermore, excessive dosage with the oestrogen causes earlier cessation of mitosis.

It has now been discovered that certain substances closely related to the sexually active hormones but themselves substantially free from sexual activity as ordinarily understood i.e. such as show substantially no activity in stimulating the secondary sex organs, are very effective for the purpose outlined above, and that, in consequence of the absence of sexual activity the disadvantages previously encountered in such preparations are avoided.

In accordance with the present invention a preparation for the treatment of human skin consists of a vehicle capable of being spread on the skin containing as active ingredient a steroid compound which is virtually free from male or female sexual activity as herein defined, and is a derivative of Δ^5-androsten-3β-ol or of Δ^4-androsten-3-one or of androstan-3β-ol or of androstan-3-one, substituted at C17 with a keto group or a hydroxyl group (in either alpha or beta position), with or

[*Price 3s. 6d.*]

without an unsubstituted alkyl group which may or may not be saturated, such compounds having 19, 20, or 21 carbon atoms (not counting the carbon atoms of any ester group present); and excluding the androgenic substances testosterone, its esters and methyl testosterone.

A first example of substance according to the invention is the inactive (non-androgenic and non-oestrogenic) stereoisomer of testosterone (Δ^4-androsten-17α-ol-3-one) known as cis-testosterone; this has proved quite satisfactory in experimental stimulation of cell mitosis in the skin.

A second example according to the invention is Δ^5-androstenediol-3β:17α.

A third example consists of 17α-ethinyl-Δ^4-androsten-17β-ol-3-one (ethinyl testosterone, commonly called ethisterone); this is virtually inactive both as an androgen and as an oestrogen, nevertheless it has proved to be fully active as a skin mitosis stimulant, better in this respect than oestrone.

In a clinical test ethisterone in a base of a cream-like consistency was applied twice daily to the skin of the arm of aged persons. After twenty one days a great change was apparent in the skin structure; there was a great increase in the epidermal thickness almost entirely confined to the layers of living uncornified cells, the outer cornified layers being relatively unaffected. The line of demarcation between the dermis and the epidermis, which is well defined in untreated senile skin, became again partially obscured, as it is in normal youthful skin, by the marginal spines of the basal cells of the stratum germinativum. The basal cells became enlarged. The dermal papillae producing the folded appearance of the dermal-epidermal junction was virtually absent in the untreated state, but after treatment the development of these papillae had returned virtually to the normal youthful state.

The above mentioned substances are also virtually inactive as an androgen or as an oestrogen, and have been proved to be fully active as skin-mitosis stimulants.

The following listed substances comprise further examples of substances which can be used according to the invention.

4. Δ^5-Androstenediol-3β-17β.
5. 17α-Methyl-Δ^5-androstenediol-3β:17β.
6. 17α-Ethyl-Δ^5-androstenediol-3β:17β.
7. 17α-Vinyl-Δ^5-androstenediol-3β:17β.
8. 17α-Ethinyl-Δ^5-androstenediol-3β:17β.
9. Androstanediol-3β:17β.
10. Androstanediol-3β:17α.
11. 17α-Methylandrostanediol-3β:17β.
12. 17α-Ethinylandrostanediol-3β:17β.
13. 17α-Vinylandrostanediol-3β:17β.
14. 17α-Ethylandrostanediol-3β:17β.
15. Androstan-17α-ol-3-one.
16. 17α-Ethinyl - androstan-17β-ol-3-one.
17. Androstan-3β-ol - 17 - one (Epiandrosterone).
18. Δ^5-Androsten-3β-ol-17-one (Dehydroepiandrosterone).

As applied to a cosmetic cream the present invention is also concerned with the nature of the cream base utilised for incorporation of the sexually inactive steroid compounds herein referred to. As heretofore compounded such creams commonly included a proportion of cholesterol, either as a specially incorporated component of the cream or as a constituent of lanolin which is frequently employed as cream base constituent. It is already known however that cholesterol promotes the absorption of lipoid soluble substances through the skin and that the removal of cholesterol from the skin and from a base or vehicle retards or inhibits such absorption.

According to a further feature of the invention therefore a cream base or vehicle for the application of the steroid substances above defined, to the skin, is made up without any cholesterol, thus ensuring that the active substances are retained in the skin and not passed to any appreciable extent into the general circulation. By these means the action of the active substances is confined for the major part to the surface layers of the skin with a consequent improvement in the efficiency of the application of the cream.

Such a cream base consists of water, glyceryl monostearate and glycerine with a minor proportion of arachis oil and of cetyl alcohol.

EXAMPLE.

A cream base consists of the following substances, the proportions being by weight:

	parts
Glyceryl monostearate -	15
Arachis oil - - -	5
Cetyl Alcohol - - -	1
Glycerine - - -	10
Water - - - -	100

The glyceryl monostearate and the glycerine are mixed with the water with a small amount of the arachis oil and cetyl alcohol, and then the rest of the last named substance added with continued mixing. In the preparation of a cosmetic cream about 10 mg. of ethisterone is then added for every ounce of the cream base.

In the case of preparations for medicinal applications other types of base or vehicle in common use, such as those having an oil base can be used.

No claim is made herein to a preparation containing any of the following compounds.

1. 17α-Ethyl-Δ^4-androsten-17β-ol-3-one (17α ethyl testosterone).
2. 17α-Vinyl-Δ^4-androsten-17β-ol - 3 - one (17α vinyl testosterone).
3. Androstan-17β-ol-3-one.
4. 17α-Methyl-androstan-17β-ol-3-one.
5. 17α-Ethyl-androstan-17β-ol-3-one.
6. 17α-Vinyl-androstan-17α-ol-3-one.

7. Androstanedione-3 : 17.
8. Δ^4-Androstenedione-3 : 17.

Subject to the foregoing disclaimer, what we claim is:—

1. A preparation for the treatment of the human skin consisting of a vehicle adapted to be spread on the skin and containing, as active ingredient, a steroid compound which is virtually free from male or female sexual activity as herein defined, and is a derivative of Δ^5-androsten-3β-ol or of Δ^4-androsten-3-one or of androstan-3β-ol or of androstan-3-one substituted at C17 with a keto group or a hydroxyl group (in either alpha or beta position), with or without an unsubstituted alkyl group which may or may not be saturated, such compounds having 19, 20 or 21 carbon atoms (not counting the carbon atoms of any ester group present); and excluding the androgenic substances testosterone, its esters and methyl testosterone.

2. A preparation for the treatment of the human skin comprising a vehicle adapted to be spread on the skin and containing as active ingredient, ethisterone (17α-ethinyl-Δ^4-androsten-17β-ol-3-one).

3. A preparation for the treatment of the human skin comprising a vehicle adapted to be spread on the skin and containing as active ingredient, Δ^5-androstenediol-3β: 17α.

4. A preparation for the treatment of the human skin comprising a vehicle adapted to be spread on the skin and containing as active ingredient any of the following substances:

1. Δ^4-Androsten-17α-ol-3-one (cis-testosterone).
2. Δ^5-Androstenediol-3β: 17β.
3. 17α-Methyl-Δ^5-androstenediol-3β: 17β.
4. 17α-Ethyl-Δ^5-androstenediol-3β: 17β.
5. 17α-Vinyl-Δ^5-androstenediol-3β: 17β.
6. 17α-Ethinyl-Δ^5-androstenediol-3β: 17β
7. Androstanediol-3β: 17β.
8. Androstanediol-3β: 17α.
9. 17α-Methylandrostanediol-3β: 17β.
10. 17α-Ethylandrostanediol-3β: 17β.
11. 17α-Vinylandrostanediol-3β: 17β.
12. 17α-Ethinylandrostanediol-3β: 17β.
13. Androstan-17α-ol-3-one.
14. 17α-Ethinyl-androstan-17β-ol-3-one.
15. Androstan-3β-ol-17-one (Epiandrosterone).
16. Δ^5-Androsten-3β-ol-17-one (Dehydroepiandrosterone).

5. A cosmetic cream comprising a vehicle adapted to be spread on the skin containing as an active ingredient any of the substances referred to in any of claims 2 to 4.

6. A method for producing preparations for the treatment of the human skin comprising incorporating in a vehicle adapted to be spread on the human skin, a steroid compound which is virtually free from male or female sexual activity as herein defined, and is a derivative of Δ^5-androsten-3β-ol or of Δ^4-androsten-3-one or of androstan-3β-ol or of androstan-3-one, substituted at C17 with a keto group or a hydroxyl group (in either alpha or be a position), with or without an unsubstituted alkyl group which may or may not be saturated, such compounds having 19, 20 or 21 carbon atoms (not counting the carbon atoms of any ester groups present); excluding the androgenic substances testosterone, its esters and methyl testosterone.

7. Preparations for the treatment of the human skin or a cosmetic cream for the same purpose according to any of claims 1 to 5 wherein the vehicle is in the nature of a cream not containing cholesterol which promote the absorption of lipoid soluble substances through the skin.

8. Preparations for the treatment of the human skin or a cosmetic cream according to claim 7 consisting of water, glyceryl monostearate and glycerine.

9. Preparations for the treatment of the human skin or a cosmetic cream according to the last preceding claim wherein said cream base further comprises a minor proportion of arachis oil and of cetyl alcohol.

10. Preparations for the treatment of the human skin or a cosmetic cream produced according to claim 8 or 9 further comprising about 10 mg. of active substance for each ounce of base.

11. Preparations for treatment of the human skin substantially as herein described.

12. Method for producing preparations for treatment of the human skin substantially as herein described.

BROMHEAD & CO.,
Chartered Patent Agents,
376—379, Strand, London, W.C.2.

PROVISIONAL SPECIFICATION

Improvements in preparations for the Treatment of the Human Skin

We, ORGANON LABORATORIES LIMITED, a British Company, of Brettenham House, Lancaster Place, London, W.C.2, do hereby declare this invention to be described in the following statement:—

The present invention relates to improvements in preparations for the treatment of the human skin directed to minimising or reducing the effects of ageing, particularly of the face and neck, by preventing or minimising wrinkling, dehydration and atrophy which are basically the cause of these changes.

Cosmetic creams have been available on the market which contain oestrogens, such as oestrone, oestradiol and stilboestrol and while such preparations have been effective to some extent in reducing wrinkling and reducing the other effects of ageing, mainly by stimulating skin mitosis, their use has been attended by the risk of undesirable side effects particularly on the uterus and breast and with the possibility of activating early malignant changes.

Another disadvantage of these substances is that the stimulation of the skin mitosis is only temporary; for example it has been found that after two weeks' application cessation of the stimulation occurs. This effect appears to be due to the increased size of the adrenal cortex induced by the oestrogen and it is known that the cessation of mitosis can be brought about by the adrenal hormones.

Alternative substances lacking these undesirable side effects have been sought and the use of oestradiol-17α (frequently termed "β-oestradiol") has been proposed; this substance has less sexual activity than the substances formerly used while having similar rejuvenating effect on the human skin to the more powerful oestrogens; but it has proved to be oestrogenic in large doses and moreover it is difficult to produce on a commercial scale.

It has now been discovered that certain substances closely related to the sexually active hormones but themselves substantially free from sexual activity as ordinarily understood i.e. such as show substantially no activity in stimulating the secondary sex organs, are very effective for the purpose outlined above and that, in consequence of their absence of sexual activity, the disadvantages previously encountered in such preparations are avoided.

In accordance with the present invention a preparation for the treatment of human skin consists of a suitable vehicle containing as active ingredient a steroid compound which is virtually free from male or female sexual activity as herein defined, other than compounds with adrenal cortical acivity, and is a derivative of Δ^4-androsten-3-one or of Δ^5-androsten-3β-ol, substituted in 17-position and containing 19, 20 or 21 carbon atoms, other than the carbon atoms of any ester groups present.

The active ingredient usable according to the present invention may be alternatively or in addition defined as including steroid compounds which are derivatives of Δ^4-androsten-3-one or of Δ^5-androsten-3β-ol, substituted in the 17-position by a keto group or by a hydroxyl group or by a hydroxyl group and a saturated or unsaturated alkyl group.

Preferably the said steroids are substituted in the 17-position only.

A first example of substance according to the invention is the inactive stereoisomer of testosterone (Δ^4-androstene-17α-ol-3-one) known as cis-testosterone; this has proved quite satisfactory in experimental stimulation of cell mitosis in the skin.

A second example consists of ethinyl androstenolone (commonly called ethisterone; this is virtually inactive both as an androgen and as an oestrogen, nevertheless it has proved to be fully active as a skin mitosis stimulant, comparable in this respect to oestrone. In a clinical test ethisterone in a cream base was applied twice daily to the skin of the arm of aged persons. After fourteen days a great change was apparent in the skin structure; there was a great increase in the epidermal thickness almost entirely confined to the layers of living uncornified cells, the outer cornified layers being relatively unaffected. The line of demarcation between the dermis and the epidermis, which is well defined in untreated senile skin, became again partially obscured, as it is in normal youthful skin, by the marginal spines of the basal cells of the stratum germinativum. The basal cells became enlarged and the dermal papillae producing the folded appearance of the dermal-epidermal junction was virtually absent in the untreated state, but after treatment the development of these papillae had returned virtually to the normal youthful state.

The present invention is also concerned with the nature of the cream base or vehicle utilised for incorporation of the sexually inactive steroid compounds herein referred to. As heretofore compounded such creams commonly included a proportion of cholesterol, either as a specially incorporated component of the cream or as a constituent of lanolin which is frequently employed as cream base constituent. It is already known however that cholesterol promotes the absorption of lipoid soluble substances through the skin and that the removal of cholesterol from the skin and from a cream base vehicle inhibits such absorption.

According to a further feature of the invention therefore a cream base or vehicle for the application of the steroid substances above defined to the skin, is made up without any cholesterol, thus ensuring that the active substances are retained in the skin and not passed to any appreciable extent into the general circulation. By these means the action of the active substance is confined for the major part to the surface layers of the skin with a consequent improvement in the efficiency of the application of the cream.

Such a cream base may consist mainly of water, glyceryl monostearate and glycerine with a small proportion of arachis oil and of cetyl alcohol.

In a preferred form of the invention a cream consists of a cream base as above defined with about 10 mg. of ethisterone for each ounce of the base.

BROMHEAD & CO.,
Chartered Patent Agents,
229/230, Strand, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1957.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.